Neutralization of Several Adult and Paediatric HIV-1 Subtype C Isolates using a Shortened Synthetic Derivative of gp120 Binding Aptamer Called UCLA1

INTRODUCTION

Previously, a gp120 binding RNA aptamer called 840 was isolated by Khos et al. and colleagues (Kho et al., 2003). The parental 840 aptamer was then truncated to 840t77, which possessed the minimal essential region for binding to gp120 (Dey et al., 2009a). In this study, a chemically synthesized derivative of the 840 parental aptamer, called UCLA1 (Cohen, 2008), was used for neutralization of endemic subtype C clinical isolates of HIV-1 from adult and paediatric patients and subtype B viral subtypes.

METHODS

The UCLA1 RNA aptamer was used for neutralization of a panel of HIV-1 subtype C and HIV-1 subtype B Env-pseudotyped viruses. Neutralization of HIV-1 was measured in duplicate as a reduction in luciferase gene expression after a single-round infection of TZM-bl cells with the Env-pseudotyped viruses as previously described (Gray et al., 2004). The binding affinity and dissociation constant of the aptamer were measured against HIV-1 subtype C D31/SI gp120 glycoprotein using the Biacore™ Surface Plasmon Resonance Technology (SPR) technology. Criticality of the aptamer was measured overnight in TZM-bl cells using an ATP-based luminescent assay. The therapeutic index (TI) of the aptamer was determined as a CC50 of 500nM for all the viruses tested.

RESULTS

The UCLA1 RNA aptamer was found to be biocidal to the TZM-bl cells (Figure 1) and exhibited high therapeutic indices for the tested viruses (Table 1). The aptamer exhibited high binding affinity for the subtype C gp120 with a very low % neutralization of 2.8% (Figure 2) compared to 840t77 (21.8M, Dey et al., 2009a). The aptamer neutralized 22/27 viruses within a range of 0-100% neutralization (Figure 2), with low IC50 values in the nanomolar range (Table 1). 24/27 were B3 and two were X4 subtype C viruses. The aptamer also neutralized X4 subtype B virus (HXB2) (Table 1). Representative neutralization graphs are shown in figure 4.

SUMMARY AND CONCLUSION

The UCLA1 RNA aptamer, a derivative of 840 gp120 aptamer isolated against a R5, subtype B gp120 derived from HIV-1, was used to neutralize a panel of subtype C HIV-1 isolates from both adult and chronically infected adult and paediatric patients.

The UCLA1 aptamer neutralized both R5 and X4 subtype C viruses as well as subtype B X4 viruses.

This data suggests that UCLA1 RNA aptamer binds to gp120 neutralization epitopes conserved across at least the two HIV-1 subtypes and tropisms.

The UCLA1 aptamer, with a greater % neutralization of 20%. The UCLA1 aptamer is resistant to cells, with average CC50 values of more than 500 nM, resulting in high therapeutic index despite CC50 values.

Taken together, this data suggests that the high therapeutic index and selectivity of the UCLA1 RNA aptamer against subtype C and B viruses may be due to a specific mechanism of action that distinguishes it from other HIV-1 gp120 inhibitors.

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REFERENCES